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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,998	06/14/2001	Maria Adele Pacciarini	01-270	1122

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PETER I. BERNSTEIN
BERNSTEIN, SCULLY, SCOTT, MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/786,998	PACCIARINI ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 18-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 4/27/2009 has been entered.

It is noted that claims 13-14 and 18-31 were finally rejected and the Board affirmed the rejection in its decision rendered on 2/26/2009.

The Request for Continued Examination filed 4/27/2009 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-12 and 15-17 have been canceled.

2. New Claims 32-33 have been added.

3. Claims 18-19, 25, 28 and 31 have been amended.

4. Remarks drawn to rejections under 35 USC 103(a) of record.

Claims 13-14 and 18-33 are pending in the case.

Claim Objections

Claim 13 is objected to because of the following informalities: Claim 13 recites the notation MMDX. The expansion of the notation should be recited followed by the notation within parentheses, since this is the first occurrence of the said notation. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-23 and 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new limitation "wherein said MMDX is administered as an infusion of from about 15 minutes to about 30 minutes" was added into claims 18 and 19. However, it is not clear if the administration of the drug is done only once for the said time periods or is repeated more than once such as recited in claims 24 and 25:

24. (Previously Presented) A method according to claim 18, wherein MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks.

25. (Currently Amended) A method according to claim [[18]] 26, wherein MMDX is administered as a 5-10 minute bolus every 8 weeks.

(Emphases added)

In absence of the recitation of the frequency of administration in the claims, one of ordinary skill in the art would not ascertain the claimed method steps to achieve a treatment of a liver tumor in a human. A similar recitation is also seen in instant claims 31-33.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687) in view of Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16), Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract), all prior art of record.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5). These derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). Pharmaceutical compositions of the active agent are also taught (col. 5, lines 20-27).

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). Kuhl also teaches compositions of MMDX and doxorubicin in ethanol (page 11, left column, under Materials and Methods). However, both Bargiotti and Kuhl do not teach or suggest a composition comprising MMDX and an agent like iodized oil.

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and Adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer (English abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising MMDX and iodized oil since compositions comprising the individual active agents have been taught in the prior art to be useful for treatment of tumors. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows

logically from their having been taught individually in the prior art. See In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Claims 18-33 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687) in view of Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16), Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract) and Gorbunova (Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990), all of record and Brem et al (US 5,626,862) newly cited.

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5). These derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). However, the intrahepatic route of administration and the administration of the drug for the time and frequency as recited in instant claims 24 and 25 are not specifically taught.

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). This means that methoxymorpholino doxorubicin can be used for the treatment of liver tumor/cancer and can be administered by intravenous infusion as taught by Bargiotti.

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and Adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer (English abstract).

Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract). Based on the teaching of Nakamura and Gorbunova one of ordinary skill in the art will recognize that methoxymorpholino doxorubicin in combination with lipidol (iodized oil) can be used for treating liver tumor/cancer via hepatic arterial infusion.

However, the prior art above does not expressly teach administration of the drug for the time period and frequency such as MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks or is administered as a 5-10 minute bolus every 8 weeks.

Brem et al. teach a delivery of chemotherapeutic agents for treating tumors generally. Brem et al. teach that pulse or short term infusions of chemotherapeutic agents are better than continuous infusions (col. 1, lines 38-42). Adriamycin (a closely related doxorubicin) has been suggested for administration for a period of at least a month (col. 7, line 65 and col. 8, lines 24-25). Even though this is with respect to Glioma this teaching of short term infusions and the time period can be applied to treatment of liver tumors and cancers. The time period for short term infusion and frequency can be optimized for maximum beneficial effects and is well within the skill level of the artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising methoxymorpholino doxorubicin with iodized oil

and use the same in a method of treating a human liver tumor and reducing systemic exposure as instantly claimed since such is seen to be taught in the prior art. It is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art.

One of ordinary skill in the art would have been motivated to use MMDX in hepatic artery administration since prior art recognizes that hepatic artery administration of doxorubicin is beneficial in treating tumor and reducing systemic exposure. Hepatic arterial administration also creates super high concentrations in the organ affected. This localized administration is beneficial for reducing systemic exposure and reducing tumor volume in the liver. One would also make a composition comprising MMDX and lipiodol (iodized oil) since lipiodol in combination with Adriamycin has shown remarkable therapeutic effects for advanced cancer as taught by Nakamura. Hence it is logical to make a composition comprising MMDX and lipiodol since MMDX is structurally close to Adriamycin and has broad spectrum antitumor activity.

Conclusion

Claims 13-14 and 18-33 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623